

# THE EXPOSOME APPROACH FOR ASSESSING THE RISKS IMPOSED BY SELECTED VOLATILE CONTAMINANTS OF ENVIRONMENTAL TOBACCO SMOKE (ETS)

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**Background and Aims:** Characterization of ETS exposure and the associated risks are subject to misclassification bias, caused by responses such as “exposure to ETS perception”, or “living with a smoker” in questionnaire-based surveys, affecting epidemiologically derived exposure risk functions. This study aims at the development of a methodological framework for assessing mechanistically the risks imposed by ETS, by evaluating biomonitoring data, internal dose modeling and Biology Based Dose Response (BBDR) modeling for three organic contaminants, namely 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone, benzene and formaldehyde, related to lung cancer, leukemia and nasopharyngeal cancer respectively.

**Methods:** A nicotine-cotinine PBPK model was developed, allowing the use of biomarkers such as urinary cotinine and nail nicotine for short and long term exposure through reverse modeling. Exposure scenarios reconstruction are fed forward to BBDR models coupling PBPK/D with mechanistic pathology modeling for each carcinogenic contaminant. Genetic polymorphisms linking variation of human susceptibility to xenobiotics were explicitly accounted for. Extrapolation to the wider population through hierarchical population modeling incorporated all variabilities and uncertainties governing exposure and response to xenobiotics from ETS.

**Results:** Individual risks estimated for lung cancer, leukemia and nasopharyngeal cancer ranged within a magnitude of order  $10^{-5}$ ,  $10^{-7}$  and  $10^{-9}$  respectively. Exposure duration had a non-linear effect on lung cancer, while the limited variability of formaldehyde exposure was compensated by the strongly non-linear mechanism governing formaldehyde-DNA adduct formation. Considering that benzene toxicity relies upon the presence of its toxic metabolites, polymorphism variability among gene variants of CYP2E1 and NQO1 was found to be determinant for overall risk assessment.

**Conclusions:** A multi-tiered approach is proposed here as a valid alternative to classic epidemiological approaches. According to the proposed methodology exposure burden is estimated based on actual biomonitoring data, individual risk is estimated using models with a strong biological underpinning and extrapolation to the wider population is done probabilistically.